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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
01/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,734	GEPSTEIN ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-177,182-186 and 196-199* is/are pending in the application.

4a) Of the above claim(s) *1-175 and 182-185* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176-177, 186, 196-199* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response to the claims filed October 7, 2008 has been received and entered. Claims 1-177, 182-186, 196-199 are pending in the application.

Election/Restrictions

Applicant's election of claims 176-195 (group IV) in the reply filed on August 17, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicants also elected cardiac specific electrical activity for claims 177 and 189 for first action on merit.

Claims 1-175 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 17, 2006. It is noted that claims 182-185 were drawn to nonelected subject matter. Therefore, claims 182-185 were also withdrawn because they are drawn to non-elected species.

Claims 176-177, 186, 196-199 drawn to an *in-vitro* culture of isolated human cells that predominantly display at least one characteristic associated with a cardiac phenotype of cardiac specific electrical activity for at least as long as a time period selected from the range of 1-60 days would be examined in the instant application. Claims 176-181, 196-199 are under examination.

Claims 176-177, 186, 196-199 are under consideration.

Maintained-Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 176-177, 186, 196-199 remain rejected under 35 U.S.C. 102 (e) as being anticipated by Funk et al. (US Patent no 6,667,176, dated 12/23/2003, filed on 10/10/2000, effective filing date 6/22/2000).

Applicant's arguments filed October 7, 2008 have been fully considered but are not persuasive.

As an initial matter it is noted that instant claims are directed to an *in vitro* culture of isolated human embryoid bodies comprising a plurality of non-cystic embryoid bodies, each including human cells exhibiting at least one characteristic associated with a cardiac phenotype. In the instant case, the breadth of the claims embrace human EB comprising plurality of non cystic EB, each including human cell showing cardiac phenotype. It was previously indicated that as recited instant *in vitro* culture comprises a mixed population of embryoid bodies comprising cystic as well as non cystic human embryoid bodies (hEB). In the instant case, claims are directed to a product and not to a product by process. Applicants' arguments as to how the product is obtained are not pertinent to the claimed product.

In response to applicants' argument that Funk et al teach culturing period of 4 days in suspension, while instant EB of present invention is produced by 7-10 days of culturing ES cells (see page 33 para. 1 and 4 of the arguments), it is emphasized that claims are directed to an *in vitro* culture of isolated EB comprising non cystic EB as well as cystic EB. Examiner would agree that Funk et al teach an isolated *in vitro* suspension culture of human embryoid bodies (EBs) that is transferred onto polyornithine-coated plates for additional 7 days that may promote differentiation. However, this does not negate the fact that culturing hES cell in

suspension for 4 days and subsequent plating on matrix would initially contain mixed populations of *in vitro* culture comprising non cystic EB and mostly cystic EB. It is noted that Funk et al reported that *in vitro* culture of human EB was examined after 7 days of plating for the presence of beating heart. Applicants' assertion of culturing of additional 8 days for identifying beating heart in all the culture is not persuasive as instant claims do not require a homogenous culture of all beating cells in the culture. Thus, *in vitro* culture of human EB on matrix coated plate after 2-7 days would contain mixed population of EB capable of differentiating into cells of different linage. The *in vitro* culture of human EB after 4 days of suspension culture disclosed by Funk and those embraced by the instant claims appear to be structurally same to the extent the culture would contain mixed population of cystic and non cystic EB, therefore, proliferation potential and cardiac phenotype including electrical activity of these would be inherently present in the cells of the non cystic EB as disclosed by Funk. As stated before, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Applicants also argue that EBs that include the cardiomyocyte progenitors show the staining of troponin which are not specific to cardiac muscle cells and that Funk et al. did not demonstrate that the cardiomyocyte progenitors of the EBs are capable of differentiating into mature cardiomyocyte (see page 34, para. 1).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., staining of troponin, mature cardiomyocyte) are not recited in the rejected claim(s). Furthermore, as such claim read on mixed population of *in vitro* culture comprising cystic and non cystic EB. Although the claims are interpreted in

light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Accordingly, Funk et al anticipates claims 176-177, 186, 196-199.

Claims 176-177, 186, 196-199 stand rejected under 35 U.S.C. 102 (e) as being anticipated by Thomson et al. (US Patent no: 7,220,584, dated 5/22/2007, filed on 8/1/2003, effective filing date 2/21/2000).

Applicants' arguments filed October 7, 2008 have been fully considered but are not persuasive.

Applicants argue that Thomson et al teaches following culture in suspension for up to 11 days, embryoid bodies are dispensed by mechanical or chemical means and can be allowed to reattach to tissue culture plates treated with gelatin or matrix, in ES medium that will form monolayer of cells. Applicants assert that such monolayer have no longer EB morphology (see page 34 and 35 of the arguments). Applicants also provide the reference of He to support that their work is distinct and not appreciated in prior art.

In response, it is noted Thomson et al teaches an *in vitro* culture of human EB containing cells that differentiate to cardiac phenotype (see claims 1-2). While, Thomson et al disclose culture of hEB in suspension for 11 days is dispensed by chemical means and is allowed to reattach to tissue culture plates treated with gelatin or matrix in ES medium (see col. 4, lines 47-52), Thompson et al also teach the non attaching colonies that coalesce into compact EB and are capable to differentiate in continuous suspension (emphasis added) (see col. 2, lines 35-37). Thompson discloses the ES cells derived from same source as one disclosed in the instant application. It is cultured in suspension culture for similar number of days as one described in the instant invention. Further, it also meets the Applicants' arguments of the importance of transferring the formed EBs to gelatin-coated plates which froze the formed EBs in the morphological state achieved by culturing under

non-adherent conditions. In the instant case, Thompson teaches culturing of hEB in suspension for 11 days and then freezing the formed EBs in the morphological state by disclosing plating EB cells on gelatin coated plate. As stated before, contrary to applicants' argument Thompson also teaches human EB could also be differentiated in continuous suspension (see col. 3, lines 35-37). Thus, in view of foregoing it is apparent that the *in vitro* culture comprising plurality of EB disclosed by Thompson and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). The resulting hEB in the *in vitro* culture would inherently contain a mixed population of cystic and non cystic hEB containing human cell having cardiac phenotype particularly since the starting cell and condition for EB formation is similar to one disclosed in the instant application.

Applicants argument of He citing the work of the applicants does not show that *in vitro* culture comprising plurality of non cystic EB were not known in prior art. It merely summarizes that among mixed population of EB some of them begin to spontaneously contract. However, it well established case law that "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical

chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Accordingly, Thomson et al anticipates claims 176-177, 186, 196-199.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 176-177, 186, 196-199 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (US Patent no: 7,220,584, dated 5/22/2007, filed on 8/1/2003, effective filing date 2/21/2000), Carpenter et al (US Patent application no 20020137204, dated 09/26/2002, filed on 10/23/2001, effective filing date 6/22/2000) and Igelmund et al (Pflugers Arch. 1999 Apr;437(5):669-79, art of record).

As an initial matter it is noted that the reference of Thompson was used for 102 rejections is used in instant obviousness rejection to meet the limitations of specific characteristics as claimed. It is emphasized that further characterization of known cells using the method of Igelmund et al would have also been obvious to one of ordinary skill in the art.

Applicants' arguments filed October 7, 2008 have been fully considered but are not persuasive. Applicants argue that Thompson for the reasons discussed in the anticipation rejection do not render obvious in combination with Carpenter and Igelmund.

In response, as stated before, Thompson et al teach culturing of hEB in suspension for 11 days and then freezing the formed EBs in the morphological state

by disclosing plating EB cells on gelatin coated plate. As stated before, contrary to applicants' argument Thompson also teaches human EB could also be differentiated in continuous suspension (see col. 3, lines 35-37). The resulting hEB culture would inherently contain a mixed population of cystic and non cystic hEB containing human cell having cardiac phenotype particularly since the starting cell and condition for EB formation is similar to one disclosed in the instant application.

Applicants' argument that the monolayer cultures have no longer EB morphology (see page 34 and 35 of the argument) is not persuasive Thompson also contemplated human EB could also be differentiated in continuous suspension (see col. 3, lines 35-37). This is further supported by the reference of Carpenter et al who disclose transferring human EBs to gelatin-coated plates after 4 days in the suspension cultures. Thus, it is apparent that one of ordinary skill in the art was aware of *in vitro* culturing of human EB in suspension culture for 4 to 11 day and then plating the human EB cell on the gelatin coated plated to freeze the formed EBs in the morphological state by culturing under the non-adherent conditions. Given that claims are broad and embrace mixed population of cystic and non cystic EB cell in the culture. It is reasonable to assert that the human EB cell cultured under suspension culture for 4-11 days (see Thompson and Carpenter para. 258 and 262) were then plated on 0.1% gelatin-coated culture dishes and observed microscopically for the appearance of spontaneous contractions. Carpenter et al teach spontaneously contracting cells in various regions of the culture after 8 days of differentiation and the number of beating regions increased up to 10^{th}. Thus, cells and method disclosed by Thompson in view of Carpenter et al appears to be morphologically and structurally similar to one disclosed in the instant application. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). The

resulting hEB in the *in vitro* culture would inherently contain a mixed population of cystic and non cystic hEB containing a human cell having cardiac phenotype particularly since the starting cell and condition for EB formation is similar to one disclosed in the instant application.

Furthermore, it would have been obvious to characterize the in vitro culture EB comprising non cystic EB, each including human cells showing cardiac phenotype. Igelmund et al (Pflugers Arch. 1999 Apr; 437(5): 669-79) teach an *in vitro* method of culturing isolate mouse EB comprising a plurality of non cytsic EB each including mouse cells exhibiting at least one characteristic associated with cardiac phenotype (see page 670, col. 1, para. 2), Specifically, Igelmund et al teach culturing mouse ES cell in suspension culture for 7 days and then plating the mouse EB on gelatin coated plate till spontaneously contracting cell cluster could be observed. It is also disclosed that the beating lasted for up to 42 days meeting the limitation of claim 198 (page 671, col. 2, para. 3). Igelmund et al also teach method to determine the spontaneous electrical activity of cardiomyocyte clusters in EBs, of small groups of cells, and of single cardiomyocytes (see page 670, col. 1, lines 2-4).

Accordingly, in view of the teachings of Thomson, Carpenter and Igelmund, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to combine the method of Igelmund et al regarding isolation and characterization of mouse EB cells comprising noncystic EB, each cell showing spontaneously contracting cells in the population of human EB comprising non cystic EB disclosed by Carpenter and Thompson to produce in vitro culture of human EB cells comprising cystic EB, each including cells showing cardiac phenotype. It is noted that all the claimed elements were known in prior art and one skilled in the art could have combined the elements as claimed by known method with no change in their respective function and the combination would have yielded nothing more than predictable results. It would have been *prima facie* obvious for one of ordinary skill in the art to replace the mouse EB with human EB

as action potential recordings from clusters of ES cell-derived cardiomyocytes within EBs would have provided in vitro chronotropy and action potential propagation of these cells for their potential use in transplantation medicine. One who would practiced the invention would have had reasonable expectation of success because Igelmund et al had already taught the method of extracellular recordings of the population action potentials of cardiomyocyte clusters to perform long-term recordings (for up to several weeks) from individual EBs under cell culture conditions. Thomson/ Carpenter taught human EB containing cardiac linage cells showing cardiac phenotype. One who would practiced the invention would have had reasonable expectation of success because Igelmund et al had already taught the method of isolating culture of mouse EB comprising plurality of non cystic EB and extracellular recordings of the population action potentials of cardiomyocyte clusters to perform long-term recordings (for up to several weeks) from individual EBs s. Thus, it would have only required routine experimentation to substitute the mouse cell with human to determine the action potential of pulsating cardiomyocytes.

It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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